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Prognostic Value of Thallium-201 Myocardial Perfusion Imaging in Patients With Unstable Angina Who Respond to Medical Treatment

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Although the prognostic value of thallium-201 imaging is well established, its ability to risk stratify patients who present with unstable angina is unclear. Fifty-two consecutive patients admitted with unstable angina who responded to medical treatment and underwent stress thallium-201 imaging within 1 week of discharge were studied. Patients were followed up for 39 ± 11 months. Cardiac events included cardiac death (n = 3), nonfatal myocardial infarction (n = 4) and admission for unstable angina or revascularization (n = 17).

The ability of thallium-201 data (redistribution, fixed defects, normal) to predict cardiac events was compared with clinical data (age, gender, prior myocardial infarction, anginal syndrome, rest and stress electrocardiogram) and cardiac catheterization data using logistic regression. Thallium-201 redistribution was the only significant predictor of cardiac death or nonfatal myocardial infarction ($p < 0.05$). The number of myocardial segments with thallium-201 redistribution ($p < 0.0005$) and a history of prior myocardial infarction ($p < 0.05$) were the only significant predictors of all cardiac events. Cardiac death or nonfatal myocardial infarction occurred more frequently in patients with thallium-201 redistribution (6 [26%] of 23) than in those without redistribution (1 [3%] of 29, $p < 0.05$). Similarly, total cardiac events developed more frequently in patients with thallium-201 redistribution ($p < 0.001$).

Stress thallium-201 imaging has important prognostic value in patients admitted with unstable angina who respond to medical therapy and can identify subgroups at high versus low risk for future cardiac events.

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The management of patients with unstable angina pectoris remains unsettled. Patients with recurrent angina despite appropriate medical treatment clearly require coronary revascularization. The more difficult management problem involves patients who "cool off" in response to in-hospital medical therapy. Although cardiac catheterization is considered to be justified in all patients with unstable angina (1), the role of revascularization is unclear. Large cooperative studies (2–4) have shown no overall survival advantage for coronary bypass surgery, although some subgroups may benefit. A noninvasive test that could distinguish high risk patients, who would be the most likely to benefit from revascularization, from low risk patients may be helpful in choosing management strategies. Thallium-201 myocardial imaging has been shown (5) to have important prognostic value in patients with a wide spectrum of coronary artery disease. Consistently, these studies (5) have found that perfusion defects showing thallium-201 redistribution, representing jeopardized viable myocardium, are associated with a high incidence of cardiac events, whereas the absence of redistribution predicts a benign outcome. Whether noninvasive risk stratification can be applied to patients presenting with unstable angina who respond to initial medical therapy without further symptoms, as it has in patients with chronic stable angina or postmyocardial infarction (5), is not known. This study was undertaken to determine whether thallium-201 imaging can distinguish high versus low risk subgroups among patients presenting with unstable angina who respond to in-hospital medical treatment.

Methods

Study patients (Table 1). The study cohort consisted of 52 consecutive patients admitted to the Medical Center Hospital of Vermont with unstable angina who underwent exercise thallium-201 myocardial imaging within 1 week of discharge between January 1984 and December 1986. Unstable angina was defined as 1) accelerating pattern of preexisting stable angina; 2) new rest angina within 8 weeks in patients with previous chronic angina; 3) new onset angina within 8 weeks in previously asymptomatic patients; and 4) prolonged episode of angina (≥20 min). Categories were not mutually exclusive. By definition, the patient cohort did not have enzymatic or electrocardiographic (ECG) evidence of myocardial infarction at the time of admission or before the thallium-201 study was performed. All patients were treated with antianginal medication, including nitrates (n = 28), beta-adrenergic (n = 24) and calcium channel (n = 33) blocking agents, and were considered by their treating

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Table 1. Clinical Variables in 52 Patients as a Function of Cardiac Events

	No Cardiac Event (n = 29)	Any Cardiac Event (n = 23)	Cardiac Death or Nonfatal MI (n = 7)
Age (yr)	62 ± 10	61 ± 11	61 ± 10
Gender (M/F)	20/9	18/5	6/1
Prior MI	12 (41%)	17 (74%)*	6 (86%)
Presenting syndrome			
Accelerating pattern	15 (52%)	11 (48%)	1 (14%)
New rest AP	7 (24%)	8 (35%)	3 (43%)
New onset AP	6 (21%)	4 (17%)	2 (29%)
Prolonged AP	7 (24%)	6 (26%)	2 (29%)
Presenting ECG			
No change	17 (59%)	11 (48%)	4 (57%)
ST ↑	2 (7%)	2 (9%)	0
ST ↓	4 (14%)	3 (13%)	3 (43%)
T wave ↓	6 (21%)	7 (30%)	0
Tl-201 results			
Normal	12 (47%)	3 (13%)	0
Redistribution	7 (24%)	16 (70%)†	6 (86%)‡
Fixed defect only	10 (34%)	4 (17%)	1 (14%)
No. of segments with RD	0.4 ± 0.9	2.0 ± 2.0§	2.1 ± 1.5
No. of fixed defect	1.6 ± 2.0	1.7 ± 2.0	2.4 ± 2.5
Exercise data			
Peak HR	138 ± 27	137 ± 23	133 ± 23
Peak BP systolic	158 ± 26	164 ± 24	156 ± 29
Exercise ECG			
Negative	20 (69%)	14 (61%)	5 (71%)
Positive	5 (17%)	6 (26%)	2 (29%)
Indeterminant	4 (14%)	3 (13%)	0
Cardiac catheterization	(n = 17)	(n = 17)	(n = 6)
0 VD	3 (18%)	1 (6%)	0
1 VD	4 (24%)	6 (35%)	2 (29%)
2 VD	5 (29%)	5 (29%)	3 (43%)
3 VD	5 (25%)	5 (29%)	1 (14%)
Ejection fraction	68 ± 14%	63 ± 15%	52 ± 9‡

*$p < 0.05$ compared with no cardiac event; †$p < 0.005$ compared with no cardiac event; ‡$p < 0.05$ compared with patients without cardiac death or nonfatal myocardial infarction (MI); §$p < 0.0001$ compared with no cardiac event. AP = angina pectoris; BP = blood pressure; ECG = electrocardiogram; F = feminine; HR = heart rate; M = masculine; RD = thallium-201 redistribution; ST ↓ or ST ↑ = ST segment depression or elevation; T wave ↓ = T wave inversion; Tl-201 = thallium-201; VD = vessel disease.

physicians to have sufficiently stabilized in response to medical treatment to allow stress thallium-201 testing and discharge without coronary revascularization. Patient characteristics, including age, gender and history of prior myocardial infarction (defined by ECG and cardiac enzyme results) were recorded.

During the period encompassed by the study, a total of 770 patients were admitted to the Medical Center Hospital of Vermont with the diagnosis of unstable angina.

Exercise protocol. Patients performed symptom-limited maximal exercise on a treadmill using the standard Bruce protocol. A positive stress ECG was defined as ≥1 mm of horizontal or downsloping ST segment depression.

Thallium-201 imaging acquisition and analysis. Cardiac imaging was performed by standard technique (6,7) in anterior, lateral and left anterior oblique projections with the patient supine. Initial and delayed (2 to 4 h) images were analyzed qualitatively and quantitatively with use of a method developed and validated at our institution (7). Briefly, each image is separated into 36 10° segments and the mean background-corrected counts within each segment is used to create relative circumferential count profiles. When compared with confidence intervals based on analysis of a normal group of subjects, areas of diminished thallium-201 uptake can be objectively defined (7,8). A segmental perfusion defect was defined as regionally decreased thallium-201 activity on the circumferential count profile of the initial image that fell below the established lower limits of normal for at least five contiguous 10° segments. All perfusion defects were defined as fixed or showing significant redistribution (6,7). Significant redistribution was defined by ≥50% improvement in minimal relative thallium-201 activity on the delayed images.

The heart was further divided into three segments on each projection: septal, inferoapical and posterior in the left anterior oblique projection and anterior, apical and inferior in the anterior and lateral projections. In addition to the presence or absence of thallium-201 redistribution, the number of myocardial segments with a defect showing redistribution and the number of segments with a fixed defect were also determined and used as potential predictors of cardiac events. Imaging results were available to treating physicians.

Coronary angiography. Standard cardiac catheterization and coronary angiography were performed for clinical indications in 34 patients. A significant coronary stenosis was defined as ≥50% luminal diameter narrowing.

Follow-up data. Follow-up data were collected using telephone interviews, physician office records and hospital records and were 100% complete. The mean follow-up period was 39 ± 11 months. Cardiac events were defined as cardiac death, nonfatal myocardial infarction or hospitalization for recurrent angina or revascularization ≥3 months after the thallium-201 study.

Statistical analysis. Values are presented as mean values ± SD. Mean values were compared with use of an unpaired *t* test. Frequency comparisons were made by using chi-square analysis and a Z test to compare proportions. Stepwise logistic regression analysis was used to compare the predictive value of thallium-201 imaging variables with that of clinical and cardiac catheterization variables.

Results

Thallium-201 imaging results. Perfusion defects that showed redistribution were seen in 23 patients. Only a fixed defect was present in 14 patients. Normal studies were seen in 15 patients.

Cardiac events (Table 1). During the follow-up period, cardiac events occurred in 23 patients: cardiac deaths in 3,

Table 2. Multivariate Predictors of Cardiac Death or Nonfatal Myocardial Infarction in 52 Patients

	Step 0: Before Variables Entered Into Model		Step 1: After Tl-201 Redistribution Entered Into Model	
	Chi-Square	p Value	Chi-Square	p Value
Presence of Tl-201 RD	5.98	0.014	(5.98)	(0.014)
Prior MI	3.29	0.07	2.36	0.09
No. of segments with thallium-201 RD	2.46	0.12	0.00	0.97
No. of fixed defects	1.32	0.25	1.83	0.22
Gender	0.73	0.39	0.43	0.51
Presence of fixed defect	0.73	0.39	1.49	0.22
Presenting syndrome	3.27	0.51	5.71	0.22
Exercise ECG	0.26	0.61	0.24	0.62
Presenting ECG	0.17	0.67	0.57	0.45
Age	0.06	0.80	0.44	0.51

Abbreviations as in Table 1. The values in parentheses refer to significant variables entered into the regression model.

Table 3. Multivariate Predictors of Overall Cardiac Events in 52 Patients

	Step 0: Before Variables Entered Into Model		Step 2: After No. of Segments With Tl-201 RD and Prior MI Entered	
	Chi-Square	p Value	Chi-Square	p Value
No. of segments with Tl-201 RD	15.05	0.0001	(14.04)	(0.0002)
Presence of Tl-201 RD	11.07	0.0009	0.22	0.64
Prior MI	5.65	0.02	(4.65)	(0.031)
Exercise ECG	4.19	0.04	0.03	0.86
Presence of fixed defect	1.96	0.16	1.07	0.30
Presenting ECG	0.67	0.41	0.64	0.42
Gender	0.57	0.45	0.02	0.88
Presenting syndrome	0.23	0.64	0.53	0.48
Age	0.05	0.83	0.17	0.68
No. of fixed defects	0.03	0.86	1.92	0.34

Abbreviations as in Table 1. The values in parentheses refer to significant variables entered into the regression model.

nonfatal myocardial infarction in 4 and admission for unstable angina or revascularization in 17.

Cardiac death and nonfatal myocardial infarction (Tables 1 and 2). Cardiac death or nonfatal myocardial infarction occurred more frequently in patients with than in patients without thallium-201 redistribution (6 [26%] of 23 versus 1 [3%] of 29, $p < 0.05$) (Table 1). No other patient variable had any significant univariate relation to these "hard" cardiac event end points. On stepwise multivariate logistic regression analysis, thallium-201 redistribution was the only significant predictor of cardiac death or nonfatal myocardial infarction (Table 2). Among the 34 patients who underwent cardiac catheterization, thallium-201 redistribution remained the only significant multivariate predictor of "hard" cardiac events ($p < 0.01$), although ejection fraction was lower in patients with a hard cardiac event.

All cardiac events (Tables 1 and 3). Overall cardiac events were more common in patients with thallium-201 redistribution ($p < 0.005$) and prior myocardial infarction ($p < 0.05$) (Table 1). Cardiac events occurred in 16 (70%) of 23 patients with thallium-201 redistribution compared with only 4 (29%) of 14 with only a fixed defect ($p < 0.05$) and 3 (20%) of 15 patients with a normal study ($p < 0.01$). In addition, the number of myocardial segments with thallium-201 redistribution was higher in patients with than in patients without a cardiac event ($p < 0.0001$). On multivariate analysis, the number of myocardial segments with thallium-201 redistribution and a history of prior myocardial infarction were the only significant predictors of total cardiac events (Table 3). Among the 34 patients who underwent cardiac catheterization, thallium-201 redistribution ($p < 0.0001$) and age ($p < 0.05$) were the only significant predictors of cardiac events.

Data were also analyzed after "low cost" variables, including age, gender, history of prior infarction, presenting anginal pattern and presenting ECG, were forced into the regression models to see what incremental value more expensive variables (such as thallium-201 imaging, ECG and cardiac catheterization data) would have in predicting cardiac events. When this approach was used, the number of segments with thallium-201 redistribution still significantly improved the ability to predict overall cardiac events ($p < 0.0002$).

Discussion

Predictive value of thallium-201 imaging. Our study shows that stress thallium-201 imaging appears to have important prognostic value in patients presenting with unstable angina who respond to initial medical therapy. Despite a selection bias in the study cohort for clinical stability, the presence of thallium-201 redistribution identified a subgroup of patients at relatively high risk for cardiac events: 26% developed the "hard" end point of cardiac death or nonfatal myocardial infarction and 70% had one of these hard end points or required readmission for unstable angina or underwent late revascularization during a mean follow-up period of approximately 3 years. In addition, the risk of overall cardiac events was related to the number of myocardial segments with thallium-201 redistribution. In contrast, patients without thallium-201 redistribution had a very benign outcome with an annual hard cardiac event rate of only 1%. Because such a group is not likely to benefit from coronary revascularization regardless of coronary anatomy, further invasive evaluation appears unwarranted.

Risk stratification with stress thallium-201 imaging may therefore have a role in choosing management strategies for patients with unstable angina who respond to medical treatment. Cardiac catheterization and possible revascularization appear justified in patients with thallium-201 redistribution, especially those with extensive areas of redistribution, because of the high risk of cardiac events. However, a more

conservative expectant approach appears warranted in patients without thallium-201 redistribution because of the very low risk of important cardiac events.

Comparison with other patient variables. Among patient variables examined, thallium-201 imaging data had the most important predictive value for future hard and soft cardiac end points. Although there was a trend toward more cardiac events among patients with a positive stress ECG, it did not reach statistical significance and this variable was not a multivariate predictor. When standard, routinely available clinical and ECG data were forced into the regression model, the presence and extent of thallium-201 redistribution retained highly significant prognostic value.

Prior studies. The results of the present study are consistent with a large body of prior work (5) demonstrating that the presence and extent of thallium-201 redistribution, a marker of jeopardized viable myocardium, predicts future cardiac events in patients with known or suspected coronary artery disease. However, there are relatively few prior data regarding thallium-201 imaging in patients with unstable angina. Hillert et al. (9) performed submaximal exercise thallium-201 imaging in patients who stabilized after admission for unstable angina. They found that 15 of 19 patients with thallium-201 redistribution developed myocardial infarction or class III or IV angina pectoris at 12 weeks after discharge compared with only 2 of 18 patients without redistribution ($p < 0.001$). The presence of a transient thallium-201 defect and abnormal stress ECG have been related (10) to risk of future myocardial infarction and cardiac death in patients who were admitted with suspected acute myocardial infarction but ruled out by serial cardiac enzyme measurements and ECGs. However, no multivariate analysis was used to examine relative predictive value in that study (10). Finally, the size of the thallium-201 perfusion defect has been shown (11) to be the best predictor of the extent of coronary artery disease in patients with unstable angina who stabilized with medical treatment, but no follow-up data were reported.

Although the pathophysiology of unstable angina is probably multifactorial, including transient platelet thrombi, coronary vasospasm or hemorrhagic rupture of an atherosclerotic plaque (12), it appears that regardless of the underlying mechanism, the presence of jeopardized viable myocardium manifest by a thallium-201 defect showing redistribution may have important value for predicting future cardiac events.

Limitations of the study. The primary limitation of the present study is the selection bias of the study cohort. Most patients in the study had undergone cardiac catheterization, yet were referred for risk stratification with thallium-201 imaging. Patients with the most severe disease may well have been sent directly to coronary revascularization. Thus, our study cohort may not reflect a general group of patients with unstable angina whose condition improves in response to medical treatment. However, it is likely that those with the most severe anatomic disease would have shown evidence of ischemia on thallium-201 imaging. Although our study cohort was selected as a relatively low risk group of patients, thallium-201 imaging still had important prognostic value, distinguishing high and low risk subgroups. Whether thallium-201 imaging would have the same predictive value in a more general population of patients with unstable angina requires further study. Furthermore, the cohort represented only a small fraction of all patients admitted with unstable angina. This likely reflected a strong bias among treating physicians at our institution during the period of the study that all patients with unstable angina should be managed aggressively and were not suitable for noninvasive evaluation. The results of our study as well as previous data (3–5) showing no overall survival advantage for revascularization versus medical treatment suggest that this bias may be unfounded for those patients who respond well to initial medical treatment.

Finally, coronary angiographic results are presented simply as the number of diseased vessels. More sophisticated analysis of coronary anatomy might have had predictive value, and conclusions regarding the relative prognostic value of thallium-201 imaging and coronary angiography are limited. However, the current study was not designed to address this issue, but rather to define the potential predictive value of noninvasive evaluation.

Conclusions. Thallium-201 imaging appears to have significant prognostic value in a select group of patients presenting with unstable angina who respond to medical treatment. The presence of thallium-201 redistribution reflecting jeopardized viable myocardium identifies patients at relatively high risk for important cardiac events, whereas those without thallium-201 redistribution appear to be at very low risk for cardiac events. Further study is needed to determine whether this approach can be applied to a more general group of patients presenting with unstable angina.

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